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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,845	06/27/2001	Xavier Paliard	1681.002	3705

7590 07/11/2006

CHIRON CORPORATION  
Intellectual Property - R440  
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EXAMINER

ANGELL, JON E

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/894,845

Applicant(s)

PALIARD, XAVIER

Examiner

Jon Eric Angell

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,6,7,10-12,15-21 and 41 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,7,10-12,15-21 and 41 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/2006 has been entered.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-3, 6, 7, 10-12, 15-21 and 41 are currently pending and are examined herein.

### ***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 6, 7, 10-12, 15-19 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), and further in view of Wakita et al. (JBC, 1998, cited by Applicant), for the reasons of record (see 10/18/2005 Office Action), which are reiterated herein for convenience.

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Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczyinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that an transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the transgene was present it would be expressed in the animal).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can

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be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is “a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection” (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Claims 1-3, 6, 7, 10-12, 15-21 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), further in view of Wakita et al. (JBC, 1998, cited by Applicant) and further in view WO 97/47358 (Donnelly et al.), for the reasons of record (see 10/18/2005 Office Action) which are reiterated herein for convenience.

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As indicated above, Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczynski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that a transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the transgene was present it would be expressed in the animal), and the HCV NS5a gene was recognized in the prior art as an HCV gene which could be used to raise an immunological response to HCV in an animal (e.g., see Donnelly et al.).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can

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be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Donnelly specifically teaches a nucleic acid encoding the HCV NS5a gene (e.g., see Figure 12) which can be used to raise an immunological response to HCV in animal (e.g., see page 1, lines 16-21; page 3, lines 17-31; page 10, line 31 through page 1 line 35; page 20, lines 14-17; claims 1, 2, 15; etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to the HCV NS5a gene can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5a tolerant animal based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is “a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection” (see abstract of Wakita), and also in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

### ***Response to Arguments***

Applicant's arguments on pages 5-12 of the communication filed 4/21/2006 have been fully considered.

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In response to the rejection of claims 1-3, 6, 7, 10-12, 15-19 and 41 under 35 U.S.C. 103(a) as being unpatentable over Gorczynski in view of Nakai and further in view of Wakita, Applicant argues that Gorczynski, the primary reference cited in the Office Action, does not teach or suggest the invention as claimed and further assert that there is no motivation provided by the Examiner to combine Gorczynski with the cited secondary references, Nakai and Wakita, to arrive at the claimed invention. Applicant also argues that, even assuming, arguendo, that such motivation were present, the invention as claimed is not described in the cited combination of references, since the combination does not disclose an animal model for tolerance (1) to an infectious disease (specifically an HCV immunogen) that (2) is operative for at least one month.

With respect to the Gorczynski reference, Applicant argues that Gorczynski is directed to the injection of spleen cells, something very different and distinct from an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed. Applicant also argues that Gorczynski demonstrates tolerance to skin allografts but suggests nothing with respect to tolerance to an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed and that Gorczynski does not teach expression of an immunogen for at least one month. Applicant asserts that Gorczynski discloses a model for allograft tolerance, and does not give any direction or guidance on how to induce tolerance to any infectious agent.

With respect to the Nakai reference, Applicant argues that Nakai fails to cure the deficiencies of the Gorczynski because it does not disclose anything about HCV and fails to teach or suggest any method for inducing tolerance to an antigen in an animal model as claimed.

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Applicant argues that the human factor IX expressed is not in any way related to an antigen or immunogen from an infectious agent, specifically an HCV immunogen as claimed.

With respect to the Wakita reference, Applicant argues that Wakita also fails to cure the deficiencies of Gorczynski, either alone or in combination with Nakai.

In response to applicant's arguments against the references individually, it is respectfully pointed out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, the claimed invention is obvious in view of the teachings of the cited references (Gorczynski, Nakai and Wakita) for the reasons of record which are reiterated above. Specifically, the prior art teaches: (1) the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal (Gorczynski), (2) that a protein of interest can be expressed in the liver of an animal for more than a month using an adeno-associated viral particle encoding the protein of interest when the viral particle is delivered by portal vein delivery (Nakai; e.g., see Table 1, Figure 5, etc.), and (3) an mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection (Wakita). It would have been prima facie obvious to one of ordinary skill in the art of creating animal models for screening agents that modulate to a viral immunogen that the cited references could be combined to make the claimed invention with a reasonable expectation of success. Furthermore, one of ordinary skill in the art would understand that making such animal models would be desirable based on the teaching of Wakita that a transgenic mouse that expresses HCV

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genes in the liver can be used as a model for to understand immunological phenomena in HCV infections (as indicated above).

Applicant also argues that Wakita teaches away from the claimed invention, in that the Cre/loxP system is used to control expression of HCV transgenes such that antigens are produced only transiently, as opposed to sustained expression for at least one month as claimed. Applicant also argues that, as opposed to generating a "tolerant" animal model, Wakita clearly states that at a minimum, an antibody response was produced in response to the transient expression of HCV antigens.

In response, it is acknowledged that Wakita only teaches transient expression of HCV transgenes. However, it is respectfully pointed out that Nakai teaches a method for sustained expression of a transgene in the liver of an animal for more than a month. It is also acknowledged that Wakita does not teach that the animal that transiently expresses the HCV transgene is a "tolerant" animal model. However, Wakita does explicitly teach that conditional transgene expression of HCV transgenes in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. Furthermore, Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal, and Nakai teaches a method for sustained expression of a transgene in the liver of an animal for more than a month. Therefore, considering the teachings of the prior art as a whole, the prior art taught all of the limitations of

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the claims, there was sufficient motivation to one of ordinary skill in the art to combine the teachings and there was a reasonable expectation of success.

Applicant submits that the cited references do not disclose or suggest all the limitations of the present invention, especially since none of the references suggests sustained expression for at least one month of an antigen from an infectious agent, in particular an HCV immunogen. Applicant asserts that since the references together do not include all of the recited claim elements, a prima facie case of obviousness has not been established. Applicant also contends that, even assuming, arguendo, that the cited references did together disclose all of the claim limitations, the Examiner has not provided any evidence indicating a motivation (either in the references or from the level of ordinary skill in the art at the time of filing) which would have provided reasonable expectation of success in combining the references to arrive at the claimed invention.

In response, it is respectfully submitted that the cited references, as a whole, do teach all of the limitations of the claims. Specifically, Wakita teaches that a mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection, Nakai teaches a method for long term expression of a transgene in the liver of a mouse and Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

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Applicants asserts that it is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims cannot be predicated on mere identification in a reference of individual components of claimed limitations. Applicant submits that in this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references (*In re Kotzab* 217 F.3d 1365, 55 USPQZd 1313, 1317 (CAFC 2000)).

In response, in the instant case the prior art has been considered in the context of the teaching of the entire reference (and in the context of all references cited), and that rejection of claims are not predicated on the mere identification in a reference of individual components of claimed limitations. Rather, the rejection is predicated on the teaching of the prior art, as a whole.

Applicant states that virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQZd 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQZd 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

In response, a high level of skill in the art is not relied on to overcome the differences between the selected elements in the references. Rather the rejection is based on the knowledge

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of one of ordinary skill in the art, and the rejection does not rely on a high level of skill in the art to provide the necessary motivation.

Applicant (citing MPEP 2143.01) asserts that the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. Applicant contends that since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

In response, it is respectfully pointed out that MPEP 2143.01 indicates:

“There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art.” *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.)...

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. “The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992)...

In the instant case, the combined teachings, the knowledge of one of *ordinary* skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of

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ordinary skill in the art that the cited references could be combined to make the claimed invention with a reasonable expectation of success. One of ordinary skill in the art would recognize the desirability for creating a mouse that expresses HCV transgenes in its liver for an extended period of time (i.e., more than a month) to create a animal model that is a powerful tool for investigating the immune responses and pathogenesis of HCV infection.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Wakita that an animal that expresses an HCV transgene in its liver is an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" provides the motivation for combining the references. Furthermore, one of ordinary skill in the art would have the knowledge to recognize that portal injection of a vector that expresses a protein is a convenient way of producing an animal that expresses a foreign gene, thus providing further suggestion and motivation to combine the references.

Applicant argues that even assuming that the references together encompass all of the claim limitations, there has not been a demonstration of an expectation of success in combining

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the elements. Applicant asserts that: [A] Gorczynski does not teach or suggest (1) sustained expression of (2) an HCV immunogen for (3) at least one month, [B] Nakai does not teach or suggest sustained expression of an HCV immunogen for at least one month, and [C] Wakita also does not teach or suggest sustained expression of an HCV immunogen for at least one month. Applicant argues that contrary to the Examiner's assertions, none of the cited references teach or suggest two essential limitations of the claims: (1) sustained expression for at least one month of (2) an HCV immunogen.

In response, it is respectfully submitted that the cited references, as a whole, do teach all of the limitations of the claims. Specifically, Wakita teaches that a mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection, Nakai teaches a method for long term expression of a transgene in the liver of a mouse and Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

With respect to the rejection of claims 1-3, 6, 7, 10-12, 15-21 and 41 under 35 U.S.C. 103(a) as being unpatentable over Gorczynski, in view of Nakai, Wakita and Donnelly. Applicants argue that there is nothing in the Donnelly reference to cure the deficiencies of Gorczynski, Nakai, and Wakita. Applicants assert that Donnelly is silent on the expression of antigens to induce immunological tolerance to HCV antigens and is instead directed to expression of HCV antigens and contend that Donnelly fails to teach or suggest anything regarding nucleic acid immunization by injection in the portal vein, or sustained expression of

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antigens in the liver to achieve immunological tolerance. Applicant respectfully submit that the combined references do not encompass all of the claimed limitations, since none of the references teach or suggest sustained expression of an HCV immunogen for at least one month to induce tolerance to the immunogen. Applicant also argues that, even assuming *arguendo*, that the combination of references did teach or suggest all of the claimed limitations, the Examiner has failed to identify the motivation for combining the references.

In response to applicant's arguments against the references individually, it is respectfully pointed out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Wakita that an animal that expresses an HCV transgene in its liver is an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" provides the motivation for combining the references. Furthermore, one of ordinary skill in the art would have the knowledge to recognize that portal injection of a vector that expresses a protein is a convenient way of producing an animal that

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expresses a foreign gene, thus providing further suggestion and motivation to combine the references.

Furthermore, it is respectfully pointed out that it is the teaching of the prior art as a whole which must be considered, as indicated above. Specifically, Wakita teaches that an mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection, Donnelly teaches that the HCV NS5a gene is an HCV immunogen which can be used to raise an immunological response in animal, Nakai teaches a method for long term expression of a transgene in the liver of a mouse and Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Furthermore, as indicated above, one of ordinary skill in the art would have been motivated to combine the teachings or the prior to make an HCV NS5a tolerant animal based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract), and in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

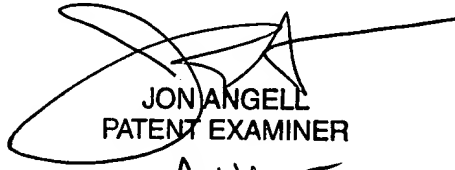
### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
JON ANGELL  
PATENT EXAMINER  
AU1635